PROPHYLACTIC CHEMOTHERAPY IN MALARIA*

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EXCEPT for very rare cases of human infections acquired from monkeys, the chemoprophylaxis of malaria can be reduced to one of two situations: 1) the chemotherapy of *Plasmodium falciparum* malaria and 2) the chemotherapy of the relapsing malarias, such as *P. vivax*, *P. ovale*, and *P. malariae*. Some understanding of the pathophysiology of the malaria infection is relevant to the problems of chemotherapy of malaria.

Plasmodium falciparum MALARIA

In general *P. falciparum* infections are the hard core infections and are eliminated last by eradication programs. Thus *P. falciparum* will be with us for a long time. There is no known variation in racial resistance in man, but the course of the disease varies from strain to strain of the parasite. For instance, we have compared a strain from Uganda, Africa, with the Camp strain from the Southwest Pacific. The Camp strain in nonimmune subjects often produces a rising parasitemia which attains a plateau at about 25,000 parasites/mm.^{3} This is not true of a Uganda strain, which may show an increase in parasite number until restrained by the decreased numbers of circulating red cells. In experimental subjects the parasitemia produced by this strain has reached 600,000 parasites/mm.^{3} with no indication of a halt without treatment.

The hazards of this disease are roughly correlated with the height of the parasitemia.

Repeated infections with *P. falciparum* produce a form of immunity that has sufficient force to moderate the course of new infections of the same strain. This semi-immune state has a very low mortality as com-

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pared to the significant mortality seen in the nonimmune state. Thus the strategy of prophylactic chemotherapy may not be the same in non-immunes as it is for semi-immunes.

The incubation period for *P. falciparum* is relatively short. Thus the chemotherapeutic agents which operate during the incubation period of five to seven days must be taken with great consistency because any drug failure however brief may allow merozoites to enter the red blood cell. After the red cells have been entered the disease presents an entirely new therapeutic challenge, for there seems to be little correlation between the causal prophylactic action of a drug and the suppressive action of a drug.

For this reason there is a tendency to classify antimalarial drugs according to the stage of the life cycle against which exerts its best action.[1] Thus a causal prophylactic agent works best against the tissue forms; this prevents parasitization of the blood cells. A suppressive cure should destroy blood forms. The prevention of red cell invasion by a suppressive drug is called clinical prophylaxis. Parasitization of the red cell and its consequences produces all the symptoms or signs of illness. In other words, the tissue forms of malaria are not known to produce illness.

In practice causal prophylaxis of *P. falciparum* malaria appears to be a very difficult objective. Very few agents have been developed that are capable of this effect. In fact, the same end result will come from long-acting suppressive agents and in *P. falciparum* malaria it is probably much safer to depend on suppressive cures than on an ideal prophylactic agent.

Even with the current distress about chloroquine resistance, we should remember that chloroquine when it works is a remarkably fine drug and is one which can be taken at intervals as great as once a week. Fortunately, the risk of encounter with a chloroquine-resistant strain of malaria can still be determined in part by geography. So far Africa is free of chloroquine-resistant *P. falciparum*. Table I shows the results of radical cure with chloroquine against a Uganda strain of *P. falciparum* from Africa in nonimmunes. Since these results in nonimmunes are consistent with the field experience with semi-immunes treated with chloroquine in Africa, it is not unreasonable to expect that 600 mg. of chloroquine will be a satisfactory treatment everywhere in Africa. Because chloroquine is excreted slowly and the parasitemia is slow to build

TABLE I.—THE CURATIVE RESPONSE OF A TYPICAL AFRICAN STRAIN OF *P. FALCIPARUM** TO CHLOROQUINE IN NONIMMUNE SUBJECTS

Dose of chloroquine	*Ratio of cures to treated cases*
300 mg.	4/8
450 mg.	11/11
600 mg.	2/2

*The Uganda strain of *P. falciparum* malaria.

TABLE II.—THE CURATIVE RESPONSE OF CERTAIN CHLOROQUINE-RESISTANT STRAINS OF *P. FALCIPARUM* TO HIGH DOSES OF CHLOROQUINE

Approximate curative dose of chloroquine	*Origin of strain*
5.0 gm.	Brazil
> 4.0 gm.	Cambodia
> 3.0 gm.	Thailand
3.0 gm.	Brazil
> 2.4 gm.	Venezuela
> 2.4 gm.	Columbia
> 1.5 gm.	Vietnam

The symbol > indicates that cure requires a dose greater than that cited.

up from the tissue forms, this suppressive cure can be used on a once-weekly basis for prophylaxis. This 600-mg. dose is easily tolerated and therefore would seem to be preferable to the 450-mg. dose in the interest of greater certainty of protection for nonimmunes. However experience with the variation in dose response between strains is quite limited.

In some other parts of the world the problem is more difficult. Chloroquine resistance has been observed most often in Southeast Asia and South America. At present there does not exist a single satisfactory prophylactic agent for chloroquine-resistant *P. falciparum* malaria. As can be seen from Table II, a few selected experiences[2-8] with so-called chloroquine-resistant strains give a dosage that can approach serious toxicity. Since we have equated practical prophylaxis with suppressive cure, it is apparent that individuals on any practical regimen of chloroquine will run the risk of illness from *P. falciparum*.

Generally speaking, no precise measure of the ratio of incidence of

TABLE III.—COMPARISON OF RESPONSE OF A STRAIN OF *P. FALCIPARUM* TO A SULFONAMIDE BEFORE AND AFTER INDUCED PYRIMETHAMINE RESISTANCE

	Sulfalene	*Dose*	*Recurrence*
Before pyrimethamine resistance	2.5 gm.	1 time	3/5 cases
After induced pyrimethamine resistance	1.0 gm.	1 time	2/11 cases*

*Recurrence in both cases was associated with loss of pyrimethamine resistance

resistant to nonresistant strains is available to us. Thus we can only guess at the degree of risk a given individual has of being exposed to drug-resistant malaria. It seems likely that certain strains will be chloroquine responsive, and that choloroquine will continue to have a prophylactic value in all parts of the world.

The problem of chloroquine resistance is under intense investigation at the moment; we can only offer some tentative suggestions for the prophylactic management of chloroquine resistance.

These suggestions are based on the early observations of Powell and Alving,[9] who reported a surprising degree of activity of diamino diphenyl sulfone in chloroquine-resistant *P. falciparum* infections.

The activity of the sulfones and sulfonamides has not always been considered very important. In the past the value of sulfonamides has been regarded as uncertain. Coggeshall et al.[10] found that in five patients treated with sulfadiazine two infections were unchanged by the drug and, in three infections, the parasites were eliminated.

This study with others was sufficient to lessen the enthusiasm for sulfonamides. An explanation for the variability in response of *P. falciparum* to sulfones and sulfonamides is suggested by recent studies in human volunteers. These studies are reviewed in Table III.[11] In brief they show that normal strains tend to be poorly responsive to sulfonamides. After the strain is made resistant to pyrimethamine the response to sulfonamide is greatly improved. In a nonpyrimethamine-resistant group a dose of 2.5 gm. gave a cure in only two of five subjects. In a pyrimethamine-resistant group, a dose of 1 gm. cured 9 of 11 subjects. In the first instance, the rate of parasite clearance was slow and, in the second instance, the rate of parasite clearance was rapid. The two failures in the pyrimethamine group were shown on reexamination to be

TABLE IV.—A COMPARISON OF RESPONSE BETWEEN A NORMAL STRAIN OF *P. FALCIPARUM* (UGANDA) AND A PYRIMETHAMINE-RESISTANT STRAIN OF *P. FALCIPARUM* (CAMP)

Sulfalene	*Uganda recurrences*	*Camp recurrences*
1 gm.	3/5	0/10
2.5 gm.	3/6	—

TABLE V.—THE CONCURRENCE OF PYRIMETHAMINE RESISTANCE IN STRAINS ALSO CHLOROQUINE-RESISTANT FROM REPORTS IN THE LITERATURE

	Pyrimethamine	*Chloroquine*
Malayan Camp	> 150 mg.	> 3.0 gm.
Thailand (AND)	> 150 mg.	> 1.5 gm.
Vietnam (CV)	> 150 mg.	> 1.5 gm.
Goiania (Brazil)	> 300 mg.	3.0 gm.
Para I (Brazil)	> 0.30 mg.	> 2.4 gm.
Columbian III	> 0.30 mg.	> 2.4 gm.

strains which had lost their pyrimethamine resistance.

There is little reason to suspect that there is any great qualitative difference in the sulfonamides or sulfones for that matter, as long as dose and duration of treatment are adequate. Recent studies in our laboratory showed that for suppressive cure of a sensitive strain, a sulfonamide should have a duration of action for at least three days.

A comparison of strain responses isolated from the field is available from a comparison of the Camp and Uganda strains. In Table IV[12] we see that the pyrimethamine-resistant Camp strain is quite sensitive to sulfalene as compared to the normal Uganda strain. In this study these two strains closely resemble the counterpart experience with the Uganda strain and the induced pyrimethamine resistant Uganda. Often we see a marked tendency for resistance to one drug, chloroquine, to be associated with resistance to the other drug, pyrimethamine (Table V).[13]

The finding that resistance to one drug, pyrimethamine, reduces the dose requirement for another drug, sulfalene, raises some interesting questions about mechanisms of drug action. For example, the metabolism of the parasite may be placed between the metabolism of two great groups of organisms. On the one hand, the bacteria which synthesize

TABLE VI.—THE MOST VULNERABLE POINT OF DRUG ATTACK

In strains with pyrimethamine resistance

PABA → folic Acid → folinic Acid

In strains which are not pyrimethamine resistant

Sulfonamides

pyrimethamine*

PABA → folic Acid → folinic Acid

*And other folic acid reductase inhibitors such as chloroguamide and trimethoprim.

folic acid and, on the other hand, higher animals including man, who absorb folic acid and are often sensitive to folic acid reductase inhibitors. The parasite is most dependent on folic acid synthesis when it is resistant to a reductase inhibitor. It thus resembles the bacteria. When it is not resistant to pyrimethamine, it is only partially dependent on folic acid synthesis and it somewhat resembles higher organisms.

These findings would also alter the interpretation of the often discussed synergism between sulfonamide and pyrimethamine.[14] The argument, as most frequently stated, attributes this synergism to a sequential block at two points of folic acid metabolism in the same organism (Table VI). Rather, it would seem that a given organism can be sensitive either to the inhibition of para-aminobenzoic acid or reductase. Synergism in this case would be due to the fact that only one of the two groups of organisms is affected by a given drug. The other strain is affected by the other drug.

I have strayed into a discussion of suppressive cures because I believe that a practical causal prophylactic agent against *P. falciparum* malaria must also be effective against the circulating trophozoite. There are a number of other agents for suppressive cure: quinine and trimethoprim alone, quinine in combination with pyrimethamine and the sulfonamides or sulfone. At present their use is limited to the treatment of acute attacks, because they do not have a long duration of action. Sulfone given daily can reduce the attack rate of chloroquine-resistant *P. falciparum;* it is currently in use in Vietnam.

In summary, it should be reemphasized that chloroquine is still the drug of choice for prophylaxis of *P. falciparum* infection. In those areas of the world where chloroquine resistance has appeared, chloroquine should be used with a sulfone or sulfonamide. Very recently progress

TABLE VII.—RELATION BETWEEN CURATIVE DOSE OF PYRIMETHAMINE AND THE NUMBER OF PARASITES IN PERIPHERAL BLOOD

Dose of pyrimethamine	*Highest observed parasite count/mm.³*			
	< 1,000	*1,000 to 20,000*	*20,000 to 100,000*	*> 200,000*
12.5 mg.	3/5*	0/1		
25.0 mg.	10/10	0/5		
50.0 mg.			0/2	
100.0 mg.				0/1

*Ratio of cure to treatment.

has been made by the Army in developing an oral long-acting sulfone. At this point in time, it would appear that failures would be reduced though probably not eliminated by using any of these agents. The reason for a limited number of failures in prophylaxis where a combination of chloroquine and folic acid synthetase inhibitor was used has not yet been analyzed.

Plasmodium vivax MALARIA

This malaria is the classic relapsing form; it exists in two varieties, depending on the relapse pattern. These two forms are compared in a schematic way with each other and with *falciparium malaria* in Table VIII. These differences are of some practical importance. In the case of the late relapsing form, the first relapse or even the first acute attack may occur as long as nine months after the subject has left an endemic zone. In general these late relapses will not occur with the quick relapsing *P. vivax* and they should never occur with *P. falciparum.*

For the most part, the quick relapsing *P. vivax* malarias have been encountered in the southwest Pacific area and Southeast Asia. The late relapsing forms of *P. vivax* infection have been reported from Europe, Korea, Madagascar, and the United States. This suggests that these forms have been adapted to more temperate zones and that the late relapse has the effect of keeping the infection dormant over winter.

P. vivax is also different from *P. falciparum* in that there is a very substantial difference in susceptibility toward the infection; this depends on the race of the patient. It is well documented that pure-blooded Negroes are virtually immune to *P. vivax* and that many patients with mixed Negro and white ancestry show intermediate degrees of resis-

tance. As a consequence the risk of infection to *P. vivax* and the consequent need for prophylaxis can be estimated in part by the ethnic character of the region from which the exposure is experienced.

In Haiti, for instance, *P. vivax* is rare; *P. falciparum* is common. *P. vivax* is rare or absent from West Africa.

The destruction of the late tissue forms of either quick or late relapsing *P. vivax* is often termed a radical cure. It is fortunate that *P. vivax* infections are not threatening to life. Thus failure of a drug used in causal prophylaxis will not be disastrous. In addition one may hope that the relapse pattern will terminate spontaneously at the end of the second year. Thus the major benefit to be derived from prophylaxis is freedom from illness for a period of about two years.

The primary problem of prophylaxis in this form of malaria is the destruction of the tissue stages. A drug effective against the tissue stages will terminate the relapse pattern. Unfortunately such drugs as chloroquine and quinine, which are effective against the blood stages of *P. vivax*, as well as of *P. falciparum*, are quite ineffective against the tissue stages.

At this time there appear to be only two classes of drug which have demonstrated an action against the tissue stages of *P. vivax* malaria in man. One class of drugs is the 8-amino quinolines, which have a chemical history dating back to methylene blue. The other class of drug are the folic acid reductase inhibitors of which pyrimethamine is the prototype.

Some authorities wait for evidence of infection before instituting a course of primaquine prophylaxis against the secondary tissue stages. If the risk of infection in a given individual is slight, there may be merit in this approach. Though the discomfort of acute malaria may be great, the danger of an attack of *P. vivax* infection is very small. Drug toxicity may be substantial and thus may justify a calculated gamble.

The patient may take 30 to 45 mg. of primaquine once or twice weekly for 8 weeks, or a weekly program may be maintained continuously during the entire stay in an endemic zone. In either case, chloroquine is given simultaneously to cover the risk of a parasite breakthrough. This approach has been instituted by the military services during the war in Vietnam.

A continuous 14 day course of once daily primaquine (15 mg.) and chloroquine may be used. This program probably achieves the best

therapeutic results, but it does require a cooperative patient or a controlled group of patients. This program was used with considerable effect during the Korean War.[15] In that situation, troops who were known to have a significant incidence of latent infection with a late relapsing form of *P. vivax* were available for 10 to 14 days during the trip back to the United States by ship. A substantial reduction of the incidence of *P. vivax* malaria was reported to have followed this program.

Not all studies on the efficacy of primaquine prophylaxis agree. Some general conclusions, however, seem possible: the usual experience with any regimen of primaquine, at doses less than those that produce considerable toxicity, is for failure rates to vary between 5% and 20%.

There is a suggestion from various data that the number of sporozoites inoculated accounts for part of these differences. A heavy inoculum means a lower rate of protection for a given dose. This was noticed in the early studies done during World War II with a variety of 8-amino-quinoline. When the mosquito inoculum fell below a certain arbitrary point, the cure rate of a given drug was much higher than if the inoculum were above this arbitrary level.

Another reason for a less than perfect protection rate is related to the problem of administering 8 or 14 doses of drug without fail. This is more than one can reasonably expect in a large group of subjects. It should be remembered that the drug is being pushed to its maximum effect under the most favorable circumstances and that any reduction below the optimal dose will inevitably reduce the therapeutic efficacy.

A discussion of primaquine probably requires a word about toxicity.

There may be a sizable amount of gastrointestinal distress of a degree sufficient to make some people stop taking the drug. The extent of this distress has not been measured accurately and has been the subject of controversy. Nevertheless, after long personal experience with this drug, I believe that some patients are adversely affected.

There is a real incidence of mild self-limited hemolytic anemia, caused for the most part by deficiency of glucose-6-phosphate dehydrogenase.

Many reviews have been written about the toxic effect of primaquine on the red blood cell; this information is readily accessible.[16] Suffice it to say that primaquine-induced hemolysis opened the way for

TABLE VIII.—THREE TYPES OF MALARIA

Plasmodium falciparum (no residual tissue stages)

Mosquito bite	Circulating asexual forms
↓	↑
Primary tissue stage	

Plasmodium vivax (quick relapsing)

Mosquito bite	Circulating asexual forms	Circulating asexual forms	Circulating asexual forms
↓	↑	↑	↑
Primary tissue stage	→ Secondary tissue stage	→ Secondary tissue stage	→ Secondary tissue stage

Plasmodium vivax (late relapsing)

Mosquito bite	Circulating asexual forms		Circulating asexual forms	Circulating asexual forms
↓			↑	↑
Primary tissue stage	↑ →	9 months →	→ Secondary tissue stage	→ Secondary tissue stage

the elucidation of a series of inherited enzyme deficiencies of the red cell. The Negro patient, who has great inherent resistance to *P. vivax* malaria and thus has less need for primaquine, however, is most often affected with primaquine-induced hemolysis.

This becomes a practical problem of some consequence only when one cannot withhold primaquine from patients on the basis of race. Fortunately the sensitive red cells are usually the old red cells. When these have been hemolyzed, the young replacement red cells are relatively invulnerable and the anemia decreases though administration of the drug is continued. This self-limited aspect of primaquine hemolysis in patients who have glucose-6-phosphate deficiency has made the problem much less serious than might have been expected.

While primaquine has been the most intensively studied causal prophylactic, it is also certain that pyrimethamine, chlorguanide, and other folic acid reductase inhibitors, such as trimethoprim, may share this property.

The major difficulty attending the use of pyrimethamine and chlorguanide is the ease with which they induce drug resistance. It does not seem to matter how large a dose is used. If the surviving parasites are not killed, they will show resistance to almost any tolerated dose of pyrimethamine. Here again we encounter a relation between the number of parasites and the dose of a drug required for cure. A dramatic

relation appears to exist between the number of parasites and the curative dose. This is shown in Table VII.[17] At high parasitemias a maximum dose of pyrimethamine may fail to cure.

Plasmodium ovale and *Plasmodium malariae* Malarias

P. ovale is the relapsing malaria of West Africa. From the very limited information available, this parasite appears to have a short life span, much as *P. vivax* does; probably it responds to the same drugs that cure *P. vivax* infections.

P. malariae (quartan malaria), on the other hand, may produce relapses over many years. Not only has the drug response of this species received very little attention, but it will be very difficult to measure the effectiveness of the anti-relapse or causal prophylactic action of a drug against quartan malaria because of the enormous span of time during which the infection must be observed. At this time it would seem reasonable to treat quartan malaria as if it were *P. vivax* and hope for the best.

Summary

A practical prophylactic agent in *P. falciparum* malaria should also destroy schizonts in the blood. Such a drug is chloroquine and it should probably always be used once a week by persons in areas where *P. falciparum* is endemic even though resistant strains are known to be present. In Africa the single weekly dose should be at least 600 mg. of chloroquine base.

In areas of possible cloroquine resistance, this program should be supplemented by a sulfone or sulfonamide. In doses equivalent to 2 gm. sulfadiazine per day for 3 days in one week, these drugs will protect against many chloroquine-resistant strains. The sulfone or sulfonamide may be long acting or may be given once daily. It is difficult to be more specific about doses because investigation of these compounds is not complete.

Although casual prophylaxis of *P. vivax* is still relatively unsatisfactory, a 10- to 14-day course of treatment with primaquine, or a weekly dose for 8 weeks with doses of 30 to 45 mg. will reduce sharply the risk of relapse. A somewhat more satisfactory cure rate will probably result from 14 days of continuous therapy with 15 mg. to 25 mg. daily, but this is often harder to manage.

Causal prophylaxis against *P. vivax* should be accompanied by chloroquine to protect against errors in drug administration.

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